protein or to a DNA required for cAMP-responsive gene expression, in an amount effective to increase cAMP-responsive-gene-expression in the subject and thereby improve long-term memory in the subject.--

**REMARKS**

Claims 1-28 were pending. Applicants have canceled without prejudice all non-elected claims. Claims 1 and 15 have been amended to specify SEQ ID NO:1 (or a human homologue thereof) as the amino acid sequence characteristic of a cAMP-responsive-element-binding-protein-2. Support for this amendment may be found in Figure 1 and on pages 51-52.

Applicants contend that these amendments raise no issue of new matter. Thus, claims 1, 3-6, 15, 16, and 18-22 as amended are pending.

**Rejection Under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 1, 3-6, 15-16, and 18-22 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the amendment to claim limitation "suffering from a long-term memory defect" is allegedly new matter, because the applicant did not point to support in the specification

nor could the examiner find support for the sub-generic claim limitation. The Examiner stated that the original claims are generic to the presently amended claims and application is directed to specific putative species of claim limitations.

In reply, applicants traverse the rejection and maintain that "suffering from a long-term memory defect" is supported in the application. For example, the Examiner is referred to page 14, lines 26-28 which recites "[a]nother embodiment of the present invention is a method for treating a subject with a long-term memory defect...." In addition, on page 15, lines 1-16, the specification recites many examples of such memory defects.

The phrase "suffering from a long-term memory defect" is fully supported by the specification and applicants request that the Examiner reconsider and withdraw this rejection.

**Rejection Under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 1, 3-6, 15-16, and 18-22 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for improving implicit long term memory in invertebrate animal subjects such as *Aplysia* and *Drosophila* using the methods as claimed, does not reasonably provide enablement for all subjects suffering from a long term memory defects. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner stated that it should be noted that non-associative

learning of *Aplysia* is using a reflex of sensory neuron to motor synapse. The Examiner stated that Bailey et al. fails to establish a nexus between the myriad of memory function in primates including associative learning and the *Aplysia* model. The Examiner states that the claims encompass all long term memory and the narrow scope of *Aplysia* model does not enable all long term memory as discussed in the previous office action.

The Examiner stated that the applicants argue that Bailey et al. (PNAS, 1996) disclose that an implicit form of memory storage in *Aplysia* is predictive model for memory storage in primates. The Examiner stated that the applicants cite the passage from the abstract that there is a conservation of steps in the mechanisms for learning-related synaptic plasticity which suggests the possibility of a molecular biology of cognition. However, the Examiner stated that the suggestion of possibility is not a direct nexus between the models for all long term memory as claimed. The Examiner stated that Bailey et al. (PNAS, 1996), page 13445, first column, last paragraph, teach that modern behavioral and biological studies have shown that learning and memory are not a unitary process--not a single faculty of the mind--but a family of distinct processes, each with its own rules. The Examiner stated that Bailey et al. (PNAS, 1996), page 13445, first column, last paragraph, further teach that nonassociative forms are but one of several categories of implicit or nondeclarative memory which also includes simple associative forms. The Examiner states that Bailey et al. (PNAS, 1996), page 13445, first column, last paragraph, further teach that the analysis of memory is complicated by another category of explicit or declarative memory which is the conscious recall of memory as opposed to reflexes or unconscious memory. The Examiner stated that Bailey et al. (PNAS, 1996), page 13445, first

column, last paragraph, further teach that explicit and implicit memory involve different neural circuits in the brain. The Examiner stated that invertebrates such as *Aplysia* (sea snail) and *Drosophila* (fruit fly) do not have a brain in the same sense as the mammals, vertebrates, or primates, but use series of interconnected ganglions which are clumps of nerve cells which control the specific region the ganglion is located such that there is a ganglion of nerve cells which control the gill or siphon withdrawal reflex. The Examiner stated that Bailey et al. (PNAS, 1996), page 13452, first column, next to the last paragraph, further teach that the apparent similarity in some of the molecular steps that underlie learning-related synaptic plasticity may reflect the fact that long-term memory for both implicit and explicit storage is associated with structural changes. The common mechanism in the second messenger process is the signaling for structural changes which is a small part of the overall long term memory process. The Examiner stated that the scope of the claim encompass all long term memory defects including cell deaths due to diseases such as Alzheimer's or Parkinson's in patients who do not have enough neuronal cells for the increased synaptic input which is possibly regulated by cAMP since the dead neurons are not functional. The Examiner stated that allegedly no nexus has been made to primates or diseases suffered by humans which have different etiology such as cell death.

The Examiner stated that the applicants argue that the *Aplysia* model would be predictive of the long-term memory storage in primates because Kandel et al. (JCP, 1997) concludes that the mechanisms used for storage of long-term memory may be conserved. The Examiner stated however, that Kandel et al., page 125, second column, first paragraph, also teach that there are differences in

the long term potentiation within the hippocampus cells in the early signaling which is part of memory storage although there is a common general signaling mechanism of cAMP activation. The Examiner stated that it should be noted that cAMP signaling is an ubiquitous signaling system in cells, the process of memory storage has many differences in detail. The Examiner stated that Kandel et al. (JCP, 1997) is a reference published after the filing date.

The Examiner stated that as discussed in the previous office actions, Glanzman (TIN, 1995), page 35, first column, teach that our knowledge about this relatively simple form of learning might just scratch the surface of its neurobiological complexity. The Examiner stated that Glanzman further teach that one wonders just how long it will be before we have a realistic cellular model of one of the intensively studied forms of mammalian associative learning. The Examiner stated that Glanzman places doubt as to the simplicity of the current *Aplysia* model and proposes a more complex model of the *Aplysia* model.

In reply, applicants respectfully traverse the rejection and maintain that the presently claimed invention is fully enabled by the subject specification.

The switch from short to long-term memory has been studied at the molecular level in the gill-withdrawal reflex of the marine snail *Aplysia* (see pages 1-2 of the subject specification). Although the total neurobiological complexity of *Aplysia* is not equivalent to that of primates, the examples provided in the subject specification focus on the signaling mechanism of cAMP activation, which the Examiner has conceded is common between *Aplysia* and primates. (See page 5 of the November 29, 1999 Office Action, at

lines 9-12.) The claimed invention is directed to a method which comprises administering to a subject a compound that inhibits binding of a cAMP-responsive-element-binding-protein-2 having an amino acid sequence identical to SEQ ID NO:1 or a human homologue thereof to a transcription factor protein or to a DNA required for cAMP-responsive gene expression in an amount effective to increase cAMP-responsive gene expression in the subject and thereby improve the subject's long-term memory.

With regard to Glanzman, applicants maintain that this reference does not support the Examiner's position. Glanzman characterizes the *Aplysia* system as an "important model system" (see 2nd line of abstract) and concludes that the model system has multiple neuronal mechanisms. Glanzman points out that there is another type of synaptic plasticity - Hebbian potentiation of the sensorimotor connections - that contributes to classical conditioning in *Aplysia*. This is the reasoning behind the statement on lines 5-6 from the bottom of column 1 of the first page of the reference which states in part "that the current cellular model of classical conditioning in *Aplysia* is too simple...." Taken out of context, this statement is misleading. The full reference indicates that Glanzman himself uses the *Aplysia* model system in his laboratory (see last page of reference, 1st column, 1st full paragrah) and that he has pointed to a new and different mechanism by which classical conditioning occurs in *Aplysia*. In view of this new mechanism, therefore, Glanzman contends that the traditional cellular model is "too simple."

This reference in no way supports the Examiner's position and applicants maintain that *Aplysia* is a well accepted model (even an "important" model - see Glanzman, abstract) which is predictive of

mechanisms in higher organisms, such as vertebrates.

Applicants direct the Examiner to page 20, line 29 to page 21, line 11 of the specification which states that

> [l]ong-term facilitation is a close cellular correlate to long-term memory in Aplysia. It is possible, therefore, that CREB2 blocks the transition from short-term memory to long-term memory in both Aplysia and mammals, including humans. Certain defects in memory formation, in particular the age-related memory loss, may represent in part the inability to remove such repression.

Clearly, the present specification allows one of ordinary skill in the art to carry out the claimed invention without undue experimentation. In view of the discussion, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Rejection Under 35 U.S.C. §102**

The Examiner rejected claims 1, 3-5 and 18-21 under 35 U.S.C. §102 (a) or (b) as being anticipated by Yin et al. (1994) for the reasons set forth in the last office action.

The Examiner stated that the teachings of Yin et al. was discussed in the previous office actions.

The Examiner stated that the applicants argue that the dCREB2a and dCREB2b in Yin et al. is a CREB1. However, the Examiner stated that it should be noted that the specification on page 16, lines

13-21, defines "cAMP-response-element-binding-protein-2" to encompass variants and homologues which does not exclude the dCREB2a and dCREB2b of Yin et al. Furthermore, the Examiner stated that the claims are read in light of the specification and do not import the limitation of the specification into the claims. Furthermore, the Examiner stated that the claims are not limited by any specific structure.

The Examiner stated that the applicants' reference of Yin et al. (1995) of Exhibit 3 compares the sequences of CREB, CREM, and ATF-1. However, the Examiner stated that it is not uncommon for scientific references to compare known sequences available at the time of the invention. Furthermore, the reference of Yin et al. (1995) of Exhibit 3 does not exclude the "cAMP-response-element-binding-protein-2" defined in the specification. The Examiner stated that the applicants' reference of Bartsch et al. (1998) of Exhibit 4 compares the sequences of *Aplysia* CREB with other CREB sequences including the *Drosophila* of Yin et al. However, the Examiner states that the reference is published after the filing date of the application and does not reflect the state of the art. Furthermore, the Examiner states that the reference of Bartsch et al. (1998) of exhibit 4 does not exclude the "cAMP-response-element-binding-protein-2" defined in the specification.

In reply, applicants traverse the rejection and maintain that the claims now pending are not anticipated by Yin et al. (1994). Claims 1 and 15 have been amended to include a structural feature to characterize the cAMP-responsive-element-binding-protein-2. Specifically, applicants have introduced a reference to SEQ ID NO:1 which is an amino acid sequence of *Aplysia* CREB2 (see pages 51-52 of the subject specification). In addition, claims 1 and 15 also

refer to "human homologues thereof" which would include a human CREB2 shown to be a homologue via sequence comparison. See the subject specification on page 20, lines 21-29, for example.

Yin et al. (1994) do not disclose the amino acid sequence shown in SEQ ID NO:1 of the subject application. In fact, there is no sequence information disclosed in Yin et al. (1994) at all. Yin et al. (1994) do refer to a form of CREB1. Applicants previously submitted Yin et al. (1995) (Exhibit 3 of the Amendment submitted on July 1, 1999) wherein Figure 4 of that reference indicates that dCREB2a is homologous to the mammalian CREB1 sequence (and to CREM and ATF-1).

The "dCREB2a" and "dCREB2b" proteins disclosed by Yin et al. (1994) do not anticipate the "cAMP-responsive-element-binding-protein-2 having an amino acid sequence identical to SEQ ID NO:1" as presently claimed. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Reconsideration and allowance of the present application in view of the foregoing amendments and accompanying remarks is respectfully requested.

If the Examiner has any questions regarding this Amendment, he is cordially invited to telephone the undersigned attorney.

No fee, other than the $435.00 extension of time fee, is deemed necessary in connection with the filing of this Amendment. If any additional fee is necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M Love

John P. White
Registration No. 28,678
Jane M. Love
Registration No. 42,812
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Jane M Love 5/26/00

John P. White Date
Reg. No. 28,678
Jane M. Love
Reg. No. 42,812